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SYMPOSIUM REVIEW

Physiology of the read–write genome

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Abstract Discoveries in cytogenetics, molecular biology, and genomics have revealed that genome change is an active cell-mediated physiological process. This is distinctly at variance with the pre-DNA assumption that genetic changes arise accidentally and sporadically. The discovery that DNA changes arise as the result of regulated cell biochemistry means that the genome is best modelled as a read–write (RW) data storage system rather than a read-only memory (ROM). The evidence behind this change in thinking and a consideration of some of its implications are the subjects of this article. Specific points include the following: cells protect themselves from accidental genome change with proofreading and DNA damage repair systems; localized point mutations result from the action of specialized trans-lesion mutator DNA polymerases; cells can join broken chromosomes and generate genome rearrangements by non-homologous end-joining (NHEJ) processes in specialized subnuclear repair centres; cells have a broad variety of natural genetic engineering (NGE) functions for transporting, diversifying and reorganizing DNA sequences in ways that generate many classes of genomic novelties; natural genetic engineering functions are regulated and subject to activation by a range of challenging life history events; cells can target the action of natural genetic engineering functions to particular genome locations by a range of well-established molecular interactions, including protein binding with regulatory factors and linkage to transcription; and genome changes in cancer can usefully be considered as consequences of the loss of homeostatic control over natural genetic engineering functions.

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Abbreviations DS, double-strand; H_C, immunoglobulin heavy chain constant region; IgH, immunoglobulin heavy chain; LINE, long interspersed nucleotide element; ncRNA, non-coding RNA; NGE, natural genetic engineering; NHEJ, non-homologous end-joining; ROM, read-only memory; RW, read–write (memory); S, switch region; S_μ, switch region upstream of the heavy chain mu exon; Ung, uracil-n-glycosylase; UV, ultraviolet; WGD, whole genome duplication.

Introduction

A major accomplishment of cytogenetics and molecular biology in the 20th century was the revelation that genome repair and genome change are active cell processes. Cells write their own genome modifications (Shapiro, 2011, 2013). When pre-DNA neo-Darwinian assumptions dictated that mutations had to be random and accidental, it did not make sense to discuss the physiology of genetic changes. But now that we know about the regulated

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molecular processes that proofread, repair and modify genomic DNA, we can discuss the physiology of how cells protect the genome and write new genomic structures when appropriately stimulated.

The goals of this review will be (i) to acquaint physiologists with the wide array of regulated biochemical systems we have come to recognize that underlie both genome stability and genome change, and (ii) to relate those systems to the processes of homeostatic regulation (McClintock, 1984, 1987).

Replication proofreading and mismatch repair

Cells actively protect themselves from mistakes by the replication apparatus. There are at least two levels for which we know details of the error-avoidance systems.

Exonuclease proofreading. Cellular DNA replication complexes contain exonuclease activities that come into play when an incorrect base has been incorporated onto the nascent DNA strand (Perrino & Loeb, 1989; Fazlieva *et al.* 2009; Ibarra *et al.* 2009). The polymerase function of a replication complex arrests when a mismatched duplex has been formed so that the exonuclease activity can remove the most recently incorporated nucleotides. Following exonuclease excision, polymerization resumes to extend the nascent strand without misincorporation. Studies with *Escherichia coli* indicate that exonuclease proofreading removes about 99.9% of the accidental misincorporations from the nascent strand (Kunkel & Bebenek, 2000).

Post-replication mismatch repair. For those misincorporations that escape exonuclease proofreading, cells have a backup mismatch repair system (Modrich & Lahue, 1996; Hays *et al.* 2005; Jiricny, 2006; Modrich, 2006; Fukui, 2010). The mismatch repair system employs duplex monitoring molecules named MutS (the *E. coli* model) or a eukaryotic homologue, such as MutSH1–6 for humans. When MutS detects a mismatch, it recruits MutL (*E. coli*) or one of its eukaryotic homologues plus an endonuclease activity to cleave the newly replicated strand on either side of the mismatch, a helicase to remove the error-containing oiligonucleotide and a repair polymerase plus ligase to produce an error-free duplex. In *E. coli*, discrimination of new and template strands occurs by detecting DNA hemimethylations (Modrich & Lahue, 1996). It is not yet clear how the strands are discriminated in eukaryotes. Mismatch repair in *E. coli* removes about 99% of the post-replication incorporation errors (Kunkel & Bebenek, 2000).

In summary, exonuclease proofreading plus mismatch repair can reduce error-driven mutations by five orders of magnitude in *E. coli* (and presumably by a similar degree in other organisms). These two physiological processes are homeostatic and respond to molecular sensing of double helix distortions.

DNA damage repair systems

Genomes are sensitive to damage by a number of physical and chemical agents, including the reactive products of oxidative metabolism in all aerobic organisms (Walker, 2000; Guetens *et al.* 2002). A variety of repair systems have evolved to deal with these external sources of genome change. The homeostatic nature of these systems was recognized as early as the 1930s.

McClintock and X-ray-induced 'mutations'. The first demonstration of cell-mediated repair of induced genome change arose out of McClintock's cytogenetic investigations of X-ray-induced maize mutants in the 1930s (McClintock, 1932). She studied the mutant strains collected by Stadler at the University of Missouri. Rather than the presumed 'gene mutations', she found that the mutants carried chromosome rearrangements. Some mutants had an unstable 'variegating' phenotype. McClintock hypothesized that variegation resulted from mitotic instability of ring chromosomes formed by joining of X-ray-induced breaks near the telomeres of a single chromosome. Although colleagues ridiculed her hypothesis, she demonstrated the postulated ring chromomes cytologically (McClintock, 1932) and went on to demonstrate that two broken chromosome ends are joined together with great efficiency in maize embryos (McClintock, 1939, 1942).

It is worth quoting McClintock's comments on these experiments in her 1983 Nobel Prize lecture because she emphasized homeostasis, cell monitoring of its genome and informed physiological responses to unpredictable genome damage events:

> 'The conclusion seems inescapable that cells are able to sense the presence in their nuclei of ruptured ends of chromosomes and then to activate a mechanism that will bring together and then unite these ends, one with another... The ability of a cell to sense these broken ends, to direct them toward each other, and then to unite them so that the union of the two DNA strands is correctly oriented, is a particularly revealing example of the sensitivity of cells to all that is going on within them... There must be numerous homeostatic adjustments required of cells. The sensing devices and the signals that initiate these adjustments are beyond our present ability to fathom. A goal for the future would be to determine the extent of knowledge the cell has of itself and how it utilizes this knowledge in a "thoughtful" manner when challenged' (McClintock, 1984).

Damage-specific repair systems. Joining two duplexes with double-strand (DS) breaks at their ends is today

Table 1. Some repair processes for distinct kinds of DNA damage (from Shapiro, 2013, with references added)

DNA damage type or agent	Error-free repair	Error-prone/mutagenic repair	References
Ionizing radiation, double-strand (DS) breakage, replication fork collapse	Homologous recombination (Rec)	Non-homologous end-joining (NHEJ)	(Cox, 2001; Lusetti & Cox, 2002; Pastwa & Blasiak, 2003; Frankenberg-Schwager *et al.* 2008; Fattah *et al.* 2010; Kass & Jasin, 2010; Grabarz *et al.* 2012; Kurosawa *et al.* 2013)
UV radiation (thymine dimers)	Nucleotide excision repair (NER)	Lesion bypass repair	(Petit & Sancar, 1999; Tang *et al.* 1999; Sutton *et al.* 2000; Walker, 2000; Goodman, 2002; Rechkunova & Lavrik, 2010)
Alkylation damage	Base excision repair (BER), NER, dealkylation	Lesion bypass repair	(Fromme & Verdine, 2004; Robertson *et al.* 2009; Kondo *et al.* 2010; Jacobs & Schar, 2012)
Large chemical adducts (e.g. benzpyrene damage)		Lesion bypass repair (DNA PolIV and V in *E. coli*)	(Wagner *et al.* 1999; Napolitano *et al.* 2000; Goodman, 2002)
Oxidative damage	BER	Lesion bypass repair	(Lu *et al.* 2001; Fromme & Verdine, 2004; Yamada *et al.* 2006; Wirtz *et al.* 2010; Jacobs & Schar, 2012)
Cytosine deamination to uracil	BER (uracil-n-glycosylase)	BER (uracil-n-glycosylase)	(Jacobs & Schar, 2012; Perez-Duran *et al.* 2012; Li *et al.* 2013)

Note that BER removal of uracil from DNA can have both mutation-prevention and mutation-promotion consequences (Perez-Duran *et al.* 2012; Li *et al.* 2013). Resolving what conditions distinguish these two situations is an active topic of investigation.

called 'non-homologous end joining' (NHEJ), and cells have various biochemical systems for carrying it out (van Gent *et al.* 2001; Pitcher *et al.* 2005; Bowater & Doherty, 2006; van Gent & van der Burg, 2007; Bennardo *et al.* 2008; Brissett & Doherty, 2009). NHEJ is but one of a series of biochemical systems that have evolved to protect genomes from many kinds of physical and chemical damage. The partial list in Table 1 gives an idea of how extensive and sophisticated the physiology of DNA damage repair has evolved to be. We will return later to the significance of error-free and error-prone repair modalities.

DNA damage checkpoints. Critical to the operation of DNA repair systems is the ability cells have to delay progress through the cell cycle until repair is complete. The physiological process of monitoring each task in the cell cycle and controlling the overall cycle so that it remains synchronized is called a 'checkpoint' (Hartwell & Weinert, 1989; Elledge, 1996).

The first checkpoint to be explicitly recognized as such was the inhibition of entry into the mitotic cell division phase following DNA damage in budding yeast (Weinert & Hartwell, 1988, 1989). If division occurs before repair is complete, non-viable daughter cells form with incomplete genomes. A similar cell division control had long been known in the *E. coli* SOS response to ultraviolet (UV) irradiation (Huisman *et al.* 1984; Schoemaker *et al.* 1984; Freudl *et al.* 1987).

We know about checkpoint controls monitoring many different aspects of the cell cycle, including genome damage (Ishikawa *et al.* 2006), replication status (Weinert, 1992; Navas *et al.* 1995; Segurado & Tercero, 2009), chromosome positioning and alignment on the spindle pole (Hoyt, 2001; Taylor *et al.* 2004; Varetti & Musacchio, 2008; Nezi & Musacchio, 2009), and cell size (Rupes *et al.* 2001; Fang *et al.* 2006; Sabelli *et al.* 2013). The reason checkpoints are so important is that they exemplify at the molecular level the processes of self-evaluation and self-control that McClintock emphasized in her Nobel Prize lecture.

Apoptosis decisions in response to DNA damage. An evaluation of both intracellular and extracellular information occurs when cells have to decide between undergoing either genome repair or programmed cell death (apoptosis) in response to DNA damage (Zmasek *et al.* 2007; Schlereth *et al.* 2010; Tentner *et al.* 2012). There are apoptosis-promoting intercellular signals in both prokaryotes (Engelberg-Kulka *et al.* 2006; Kolodkin-Gal *et al.* 2007; Kolodkin-Gal & Engelberg-Kulka, 2008) and eukaryotes (Yin, 2000; Krieghoff-Henning & Hofmann, 2008; Walsh & Edinger, 2010). In mammalian cell culture, the presence of growth factors (such as insulin-like growth factor, IGF) protects against apoptosis and leads to a DNA repair response, while the presence of 'death factors' (such as tumour necrosis factor, TNF) induces an apoptotic response (Remacle-Bonnet *et al.* 2000; Danielsen &

Maihle, 2002; Linseman *et al.* 2002; Janes *et al.* 2005; Gomez-Vicente *et al.* 2006; Song, 2007; Holoch & Griffith, 2009; Joza *et al.* 2009). The ability of cells to sense their biological environment and make life-or-death decisions based on intercellular signals is a prototypical homeostatic process (Loewer & Lahav, 2006). We will see other cell signal responses when we discuss the control of molecular systems to restructure the genome.

Mutator polymerases and point mutations

In the early 1950s, it became evident that UV-induced mutagenesis in *E. coli* is an active cell process, part of what we later came to call the 'SOS' DNA damage response (Witkin, 1975, 1991; Little & Mount, 1982). Jean Weigle, a Swiss physicist turned molecular biologist, performed the clarifying experiments (Weigle, 1953; Weigle & Bertani, 1953). He used bacterial virus 'lambda' as his test organism. The advantage of a virus was that the test DNA could be treated independently of the cells in which it replicated and mutated by irradiating cell-free suspensions of lambda prior to infection.

Weigle systematically tested all combinations of untreated and irradiated virus and host cells. He found that irradiated cells had much greater capacity both to repair lethal damage and also to induce mutations in the irradiated lambda genomes. To universal surprise, he also found augmented mutagenesis in untreated virus infecting irradiated cells. In other words, UV irradiation induced mutagenesis activity in the host cells, active even on unirradiated DNA. This activity was dubbed 'error-prone' repair (Witkin, 1973).

Error-free and error-prone repair. The notion that certain repair processes are precise and 'error-free' whereas others are imprecise and 'error-prone' (Table 1) is based on considering repair as the chief evolved functionality. The distinction works readily for cases such as DS break repair. For broken duplexes, repair by the multi-step process of homologous recombination with an undamaged template is intrinsically error-free (Kowalczykowski *et al.* 1994; Kowalczykowski, 2000). NHEJ, by contrast, generally creates new sequence structures and is therefore inherently error-prone and mutagenic (Lieber, 2010; Symington & Gautier, 2011).

In other cases, the distinction between error-prone and dedicated mutator function is less clear. For example, as indicated in Table 1, base excision repair removal of uracil from DNA by uracil-n-glycosylase (Ung) activity can lead either to accurate repair, as in *E. coli*, or to mutagenic repair, as in activated B lymphocytes. In the immune system, Ung activity is essential to somatic hypermutation for antibody refinement (Perez-Duran *et al.* 2012). Similarly, the UV-inducible *E. coli* SOS functions DinB and UmuCD play key roles in mutagenesis, but their absence has little effect on bacterial repair capacity (Maenhaut-Michel, 1985; Brotcorne-Lannoye & Maenhaut-Michel, 1986). Does this mean that some SOS activities act more as mutator than repair functions (Goodman, 1998; Garcia-Diaz *et al.* 2003; McKenzie *et al.* 2003; Galhardo *et al.* 2009)?

Trans-lesion bypass 'mutator' polymerases. An ambiguous answer to the question about UmuCD and DinB mutator function comes from the discovery that they represent a new class of DNA polymerase activity. DinB encodes DNA polymerase IV, and UmuCD encodes DNA polymerase V (Reuven *et al.* 1999; Wagner *et al.* 1999).

PolIV and PolV typify a class of non-processive polymerases that have the capacity to elongate nascent DNA strands a few nucleotides opposite a damaged template strand ('trans-lesion bypass' polymerization) (Goodman, 2002). As would be expected from the ability to overcome template damage, trans-lesion bypass polymerases are highly prone to mutagenic misincorporations. Thus, they have also been called 'mutator DNA polymerases' (McKenzie & Rosenberg, 2001).

Detailed study of UV-induced mutagenesis in *E. coli* revealed that particular trans-lesion polymerases (or pairs thereof) are necessary for specific kinds of mutations to occur, such as −1 or −2 frameshifts or particular base substitutions (Napolitano *et al.* 2000; Fuchs *et al.* 2001). These unexpected results indicate that individual localized point mutations are the result of action by specific biochemical functions. Certainly, this conclusion fits with the demonstrations that PolIV and PolV account for the inducible mutagenic activity that Weigle discovered on unirradiated lambda DNA (Caillet-Fauquet & Maenhaut-Michel, 1988; Maenhaut-Michel & Caillet-Fauquet, 1990; Maenhaut-Michel *et al.* 1992). The involvement of identifiable enzymes with particular DNA changes is far more in agreement with the physiological view of mutation than with the random accident assumption.

NHEJ, chromosome rearrangements and DS break repair centres

As McClintock observed over the many years that she studied the fate of broken chromosome ends, NHEJ is the source of many kinds of chromosome rearrangements. In the prior citation from her Nobel Prize lecture, she pointed out that cells must have the ability to bring broken chromosome ends together. Analysis of DS break repair in budding yeast has thrown some light on this process (Lisby *et al.* 2001, 2003*a*,*b*; Lisby & Rothstein, 2004, 2005).

When DS breaks occur in eukaryotic cells, specialized chromatin, containing the exceptional histones H2A

(yeast) or H2AX (mammals), forms at the broken ends. By using immunofluorescence and fluorescent protein tags to detect H2A, it is possible to see that broken ends, homologous recombination proteins and NHEJ proteins localize to subnuclear foci ('repair centres') in a cell cycle-dependent manner (Lisby & Rothstein, 2004). By differential labelling of nearby DNA, the presence of broken ends from two different chromosomes can be observed in a single repair centre (Lisby *et al.* 2003*b*), where the ends can be joined by NHEJ to form a translocation or other rearrangement structure.

For recombination and NHEJ to take place, motor proteins are required for two distinct tasks: (i) chromatin remodelling of the damaged DNA (Giglia-Mari *et al.* 2011; Xu *et al.* 2012; Bennett *et al.* 2013; North *et al.* 2013; Seeber *et al.* 2013) and (ii) powering the DNA movements needed for repair centre localization and execution of strand exchanges (Mazin *et al.* 2010; Ceballos & Heyer, 2011; Burgess *et al.* 2013). The nature of control over chromosome movements towards the repair centres remains unclear, but the physiological nature of DS break repair is unmistakable insofar as its cell biology is concerned.

Natural genetic engineering (NGE) functions

In addition to systems used both for DNA repair and for genome change, there are a number of evolved complex molecular systems that appear dedicated to generating novel genome structures. Table 2 lists a number of categories for these genome innovation systems.

From the list of diverse DNA transfer and rearrangement systems in Table 2, it is evident that cells have complex physiologies for assembling and modifying their genomes. The range of molecular functionalities enables living organisms to accomplish the following adaptive genome writing tasks:

Import and integrate extensive DNA segments encoding adaptive functions (horizontal transfer). The ability of cells to acquire DNA by direct uptake from the environment, virus infection, conjugal transfer, parasite vectors (Houck *et al.* 1991) or other as yet unknown means has made it possible for genomes to acquire coding capacity for new biochemical activities. The importance of horizontal DNA transfer in the spread of antibiotic resistance and specialized adaptations in bacteria and archaea is widely recognized (Grassi *et al.* 2012) (http://shapiro.bsd.uchicago.edu/ExtraRefs.AntibioticResistanceAndHorizontalTransfer.shtml). Less well known are a rapidly growing number of examples where eukaryotic microbes and multicellular eukaryotes have acquired adaptive functions from prokaryotes or other eukaryotes by horizontal DNA transfer (Kondrashov *et al.* 2006; Keeling & Palmer, 2008; Keeling, 2009; Whitaker *et al.* 2009; Danchin *et al.* 2010; Oliver *et al.* 2010; Acuna *et al.* 2012; Danchin & Rosso, 2012; Xi *et al.* 2012).

Diversify protein structures. DNA rearrangements serve the antagonistic cells providing adaptive immunity (http://shapiro.bsd.uchicago.edu/ExtraRefs.ImmuneSystemChanges.shtml) and their infectious microbial targets, which undergo surface antigen variation to escape immune system defences (Wisniewski-Dye & Vial, 2008; Deitsch *et al.* 2009; Cahoon & Seifert, 2011). In addition, site-specific recombination 'shufflons' serve to expand pilus attachment specificity for plasmid transfer (Gyohda *et al.* 2004), and 'diversity-generating retroelements' extend bacteriophage host range (Doulatov *et al.* 2004).

Alter the regulation of existing functions. Insertion of a mobile genetic element in or near a particular genetic locus is among the most common ways of altering regulation of an existing genetic locus (Nakayashiki, 2011) (http://shapiro.bsd.uchicago.edu/Table4B(4).MoreFormattingofInsertionTargetsbyMobileGeneticElements.html). The regulatory changes include transcription factor-, micro RNA- and RNA-directed epigenetic controls. There are numerous examples of transcription factor regulatory sites mobilized by transposons, retrotransposons and retroviruses (http://shapiro.bsd.uchicago.edu/Table5C-1.MobileElementsFoundtobeExaptedascis-RegulatoryControlSitesinAnimals.html), and epigenetic imprinting is often linked to the presence of DNA from mobile elements (Youngson *et al.* 2005; Kinoshita *et al.* 2007; Suzuki *et al.* 2007; Fujimoto *et al.* 2008; Gehring *et al.* 2009; Pask *et al.* 2009; Cowley *et al.* 2011).

In addition to mobile elements, integrated viruses also change the regulatory configuration of the genome (Kokosar & Kordis, 2013). Viruses provide sequences for non-coding (ncRNAs) (Frias-Lasserre, 2012), sites for transcriptional control (Peaston *et al.* 2004; Dunn *et al.* 2005; Maksakova *et al.* 2006; Conley *et al.* 2008; Jern & Coffin, 2008; Cohen *et al.* 2009; Beyer *et al.* 2011) and epigenetic regulation (Brunmeir *et al.* 2010; Macfarlan *et al.* 2011; Conley & Jordan, 2012; Ward *et al.* 2013).

Shuffle exons to generate novel multi-domain protein activities. It has become apparent from genome sequencing that many new protein functionalities arise from the accretion and rearrangement of functional 'domains' shared by many different proteins (Doolittle & Bork, 1993; Doolittle, 1995; Lander *et al.* 2001; Toll-Riera & Alba, 2013). There is direct evidence in several species that mobile genetic elements have mediated exon shuffling in the past and can do so experimentally in real time

Table 2. Genome restructuring natural genetic engineering (NGE) systems

Function	System	References
Horizontal nucleic acid transfer between cells	DNA import and export complexes	(Zupan *et al.* 2000; Chen & Dubnau, 2004; Cehovin *et al.* 2013)
	Plasmids and other conjugative elements	(Hayes, 1968; Sonea, 1987; Smillie *et al.* 2010; Leclercq *et al.* 2012)
	Viruses	(Forterre, 2006; Comeau *et al.* 2008; Forterre, 2010; Krupovic *et al.* 2011)
	Virus-like 'gene transfer agents' (GTAs)	(Lang & Beatty, 2007; Stanton, 2007; Zhao *et al.* 2009; Leung *et al.* 2010)
Generate copies or variants of genome coding sequences	Reverse transcription and genome insertion of processed RNAs	(Brosius, 2003; Baertsch *et al.* 2008)
Mobilize DNA segments within and between molecules	Site-specific recombination systems	(Landy, 1989; Hall & Stokes, 1993; Grindley *et al.* 2006; Cambray *et al.* 2010; Hallet & Sherratt, 2010)
	DNA transposons	(Curcio & Derbyshire, 2003)
	Retroviruses and retroviral-like LTR retrotransposons	(McDonald *et al.* 1997; Rho *et al.* 2007; Novikova, 2009)
	Non-LTR retrotransposons	(Schmidt, 1999; Han, 2010)
	Inteins	(Elleuche & Poggeler, 2010)
	Retrosplicing introns	(Lambowitz & Zimmerly, 2011)
Generate diversity in protein structure or expression	Silent cassette conversion into expression sites	(Plasterk *et al.* 1985; Barry & McCulloch, 2001; Horn, 2004; Barbour *et al.* 2006; Cahoon & Seifert, 2011)
	Shufflons and invertons	(Komano, 1999; Hallet & Sherratt, 2010)
	Diversity-generating retroelements	(Medhekar & Miller, 2007)
	Variable lymphocyte receptor diversification	(Rogozin *et al.* 2007; Boehm *et al.* 2012)
	VDJ joining	(Bassing *et al.* 2002; Alt *et al.* 2013)
	Somatic hypermutation	(Honjo *et al.* 2002; Longerich *et al.* 2006; Peled *et al.* 2008)
	Isotype class switching	(Honjo *et al.* 2002; Longerich *et al.* 2006; Bothmer *et al.* 2011; Bothmer *et al.* 2013)
Genome immunity acquisition	Clustered regular interspersed palindromic repeats (CRISPRs)	(Barrangou, 2013; Sorek *et al.* 2013)
	piRNA loci	(Brennecke *et al.* 2007; Handler *et al.* 2013)
Developmental chromatin diminution		(Muller & Tobler, 2000; Bachmann-Waldmann *et al.* 2004)
Ciliate macronucleus development	Excision of germline-specific sequences, unscrambling of jumbled coding sequences, telomere capping of short multicopy minichromosomes	(Juranek & Lipps, 2007; Nowacki *et al.* 2011)

Abbreviations: LTR, long terminal repeat; piRNA, piwi-binding RNA; VDJ, variable, diversity and join cassettes of immunoglobulin-encoding DNA sequences.

(Moran *et al.* 1999; Hiller *et al.* 2000; Ejima & Yang, 2003; Liu & Grigoriev, 2004; Morgante *et al.* 2005; Damert *et al.* 2009; Hancks *et al.* 2009; Elrouby & Bureau, 2010) (http://shapiro.bsd.uchicago.edu/Table5A.ExamplesofDocumentedExonShufflingbyMobileGeneticElements.html).

Create new polynucleotide coding sequences. One of the outstanding problems in protein evolution is the origin of novel domain and whole protein coding sequences. This problem has been partially solved by discovering (i) that new exons frequently arise post-insertion by utilization of splice signals inside mobile elements ('exonization') (Sorek, 2007; Burns & Boeke, 2008; Toll-Riera *et al.* 2009; Wissler *et al.* 2013) (http://shapiro.bsd.uchicago.edu/Origin_of_New_Protein_Domains.html) and (ii) that 'neogene' formation occurs by insertion of reversed transcribed sequences into genetic loci, often generating chimeric coding regions (Long, 2001; Betrán *et al.* 2002; Piriyapongsa *et al.* 2007; Chen *et al.* 2010; Fu *et al.* 2010; Schmitz & Brosius, 2011; Mandal *et al.* 2013) (http://shapiro.bsd.uchicago.edu/Table5B.Reportsofretrogenesinplantandanimalgenomes.html).

New coding sequences also arise by the reverse transcription and insertion of 'edited' (sequence altered) mRNAs or ncRNAs (Lev-Maor *et al.* 2007; Xie *et al.* 2012; Mandal *et al.* 2013). In addition to mobile elements, fragments of viral and organelle sequences have also undergone exonization to generate novel proteins and domains in nuclear genomes (Taylor & Bruenn, 2009; Koonin, 2010; Liu *et al.* 2010, 2011*a*,*b*; Chiba *et al.* 2011; Lloyd & Timmis, 2011; Woehle *et al.* 2011; Rousseau-Gueutin *et al.* 2012).

Enhance protein diversity by alternative transcription and splicing signals. When a mobile element inserts into an intron, it can generate transcript and protein diversity by providing both alternative transcription initiation and termination sites as well as alternative splice signals (Han *et al.* 2004; Han & Boeke, 2005; Wheelan *et al.* 2005; Zemojtel *et al.* 2007; Burns & Boeke, 2008; Gogvadze & Buzdin, 2009; Kaer *et al.* 2011). These additional regulatory sites lead to the production of messages truncated either at the 5′ start or at the 3′ tail and encoding proteins with altered combinations of exons.

Rapidly disperse common regulatory sequences to distant genetic loci to generate coordinately controlled genome networks. The ability of mobile elements to move rapidly to many genome locations allows them to solve the problem of generating functionally coordinated networks without having to alter each locus independently (Feschotte, 2008; Kunarso *et al.* 2010; Lynch *et al.* 2011) (http://shapiro.bsd.uchicago.edu/Table5C-1.MobileElementsFoundtobeExaptedascis-RegulatoryControlSitesinAnimals.html). Single events can activate mobile element activity that results in multiple genome modifications. This is of particular importance after interspecific hybridization and whole genome duplication (WGD), which create redundant copies of entire networks (Teichmann & Babu, 2004). It is noteworthy that such WGD events correspond to major transitions in the evolutionary record, such as the emergence of vertebrates (Kasahara, 2007).

Viruses as part of the distributed RW genome. Listing viruses as agents of genome transfer may appear surprising to many readers accustomed to think of these sub-cellular infectious agents as parasites. But it is also useful to consider viruses as both extracellular and intra-cellular extensions of the collective read–write (RW) genome of living cells. This view was implicit in the work of Lwoff and his students Wollman and Jacob on temperate bacteriophages, which could enter and exit from the genomes of bacteria (Lwoff, 1954, 1957, 1966; Jacob & Wollman, 1961; Wollman & Jacob, 1961). Sonea and Panisset explicitly articulated the collective genome concept for prokaryotes in the 1970s and 1980s (Sonea, 1971; Sonea & Panisset, 1983; Sonea & Mathieu, 2001).

Sonea and Panisset viewed the prokaryotic genome as an ecology-wide distributed system containing DNA sequences encoding all manner of adaptive functions. When a particular ecological niche became available, the requisite functions could be assembled in one cell by horizontal DNA transfer, including viral infections, to produce an organism that could exploit the new niche. In accordance with this view, the results of environmental metagenomics show that the virosphere provides a significant reservoir of DNA encoding a wide range of cellular functions (Williamson *et al.* 2008; Kristensen *et al.* 2010; Alperovitch-Lavy *et al.* 2011; Sharon *et al.* 2011; Breitbart, 2012; Hurwitz *et al.* 2013; Roux *et al.* 2013; Schoenfeld *et al.* 2013).

Moreover, sequencing the genomes of recently discovered giant DNA viruses that infect amoebae, algae and other protists has revealed a realm of genome mixing between the three domains of life. The megabase-range genomes of these viruses contain mixtures of viral, archaeal, bacterial and eukaryotic sequences (Boyer *et al.* 2009; Wilson *et al.* 2009; Colson & Raoult, 2010; Fischer *et al.* 2010; Yutin *et al.* 2013). Large DNA viruses have extended host ranges, and the protists they infect harbour bacterial symbionts that also infect plants and animals (Huws *et al.* 2008; Bozzaro & Eichinger, 2011; Steinert, 2011; Yousuf *et al.* 2013). There is even evidence of conjugal transfer within amoebae between animal and plant pathogenic bacteria (Saisongkorh *et al.* 2010). Thus, there exist multiple biological paths for distributing novelties originating within the lower eukaryote-cum-large DNA virus 'melting pot' for genome sequence innovation to all kinds of cells (Boyer *et al.* 2009; Moliner *et al.* 2010).

Activation of NGE

One of the major features of cell-mediated genome change is regulation over the biochemical activities involved. This means physiologically that genome change functions are facultative and responsive to external and internal stimuli (http://shapiro.bsd.uchicago.edu/TableII.7.shtml). The range of activating NGE stimuli extend from DNA damage and other stress events (infection, hybridization, starvation) to evolved responses to intercellular signals (pheromones, lymphokines).

My personal experience with physiological activation of NGE came from studying the action of a transposable element in mediating the fusion of the *araB* and *lacZ* coding sequences to direct synthesis of a hybrid protein (Shapiro, 1984, 1997). Fusions were not detectable in over 3×10^{10} plated bacteria following normal growth (i.e. no colonies within the first 3–4 days), but after several days of additional incubation colonies began to sprout in ever greater numbers, and the frequency

rapidly increased to at least one fusion per 10^5 viable bacteria on the selection plates. Fusions were dependent on transposase activity (Shapiro & Leach, 1990). The key parameter inducing this particular DNA restructuring process was aerobic starvation, independent of the initial carbon source (Maenhaut-Michel & Shapiro, 1994), and a number of regulatory proteases and transcription factors were necessary for fusion activation (Shapiro, 1993; Gomez-Gomez *et al.* 1997; Lamrani *et al.* 1999).

The *araB–lacZ* fusion system was the first example of a more general phenomenon that has come to be called 'adaptive mutation' (Foster, 1993; Shapiro, 1997; Hall, 1998; Rosenberg, 2001) (http://shapiro.bsd.uchicago.edu/TableII.7.shtml). Although the phenomenon and the term 'adaptive' have proved controversial (Roth *et al.* 2006), I argue that the term is appropriate in two senses: (i) increased mutability occurs as an *adaptive* response to starvation conditions, and (ii) among the resulting mutations, there are invariably some that provide *adaptation* to the selective conditions.

The stresses or deviations from the normal genomic state that trigger mutability in eukaryotes correlate with stimuli that alter epigenetic formatting (http://shapiro.bsd.uchicago.edu/TableII.10.shtml). It therefore appears that a major mode of NGE activation is disruption of epigenetic controls known to inhibit the activity of mobile elements and possibly other DNA restructuring functions (Hollister & Gaut, 2009; Handler *et al.* 2013; Nuthikattu *et al.* 2013). In addition to destabilizing NGE controls, perturbations of various outside inputs ranging from nutrition to maternal care lead to trans-generational epigenetic changes without altering the underlying DNA sequences (http://shapiro.bsd.uchicago.edu/Transgenerational_Epigenetic_Effects.html). How and why various stresses and stimuli affect epigenetic silencing is an active topic of research concerning physiological impacts on the genome.

As expected from physiological processes, there are a number of diverse but specific effects of intercellular signalling molecules on NGE activities. In bacteria, pheromones and quorum sensing signals stimulate transfer of conjugative elements and uptake of extracellular DNA (Fuqua & Winans, 1994; Auchtung *et al.* 2005; Meibom *et al.* 2005; Kozlowicz *et al.* 2006*a*,*b*; Dunny, 2007; Christie-Oleza *et al.* 2009; Suckow *et al.* 2011; Lo Scrudato & Blokesch, 2012; Cook & Federle, 2013). In budding yeast, retrotransposition of the Ty3 and Ty5 elements is coordinated with mating events by sex pheromone induction (Kinsey & Sandmeyer, 1995; Ke *et al.* 1997). In rodents, steroid hormones induce reproduction and retrotransposition of mouse mammary tumour virus (Truss *et al.* 1992). In the mouse and human immune systems, lymphokine molecules determine the sites of DS breaks and NHEJ for isotype switching (Kinoshita *et al.* 1998; Dunnick *et al.* 2011).

Cell- and tissue-type specific NGE processes as part of the normal life cycle

The DNA changes associated with antigen receptor synthesis in lymphocytes are the most thoroughly documented case of a tissue-specific NGE process (http://shapiro.bsd.uchicago.edu/ExtraRefs.ImmuneSystemChanges.shtml). But there are other cases, which show that the immune system is far from exceptional. In *Drosophila* and nematodes, for example, the actions of P factors and other mobile genetic elements are specific to germ-line tissues (Laski *et al.* 1986; Siebel & Rio, 1990; Moerman *et al.* 1991; Takeda *et al.* 2007; Koga *et al.* 2008; Keng *et al.* 2009). The same germ-line restriction is true of a retrotransposon in mice (Dupressoir & Heidmann, 1996).

One of the more intriguing tissue-specific regulatory phenomena is the activation of long interspersed element (LINE) retrotransposition in mammalian neural cells (Muotri *et al.* 2005, 2010; Coufal *et al.* 2009; Thomas *et al.* 2012). This observation has led to the hypothesis that LINE-induced genome diversity is a contributing factor to neural network architecture in the mammalian nervous system (Muotri & Gage, 2006; Muotri *et al.* 2007). There is also the potential for deleterious changes, and a recent report links LINE retrotransposition to schizophrenia (Bundo *et al.* 2014).

Targeting of NGE

The ability of cells to regulate NGE functions is not limited to turning them on and off. Cells employ a range of different molecular mechanisms to target NGE activity both towards and away from particular regions of the genome (http://shapiro.bsd.uchicago.edu/TableII.11.shtml). The targeting mechanisms involve familiar molecular interactions: protein–DNA sequence binding, protein–protein binding, nucleic acid sequence homologies and coupling to transcription. What has made recognition of this widespread targeting capacity difficult for many biologists to accept is simply the unsupported *ad hoc* assertion that such targeting within the genome is not possible. A very partial discussion of targeting examples follows.

Homologous recombination. In principle, homologous recombination can occur between any two DNA duplexes that have the same sequence. But the real *in vivo* recombination process inevitably displays non-uniformity across the genome ('hotspots' and 'coldspots') (Smith, 1994; Huang & Keil, 1995; Amundsen & Smith, 2007; Cromie *et al.* 2007; Grey *et al.* 2009; Brunschwig *et al.* 2012; Steiner & Steiner, 2012; Martin-Castellanos *et al.* 2013). The non-uniformity reflects the biochemical complexity of the homologous exchange process (Kowalczykowski *et al.* 1994; Kowalczykowski, 2000; San Filippo *et al.* 2008),

which provides opportunities for regulation, as well as the need for specific protein–DNA interactions to carry out the actual physiological recombination steps (Krejci *et al.* 2012; Baudat *et al.* 2013).

An example of sequence specificity is provided by the 'chi' sites regulating motor protein behaviour and exonuclease specificity of proteins needed to process broken duplex ends to initiate bacterial recombination (Spies *et al.* 2003; Amundsen & Smith, 2007). This feature of the prokaryotic recombination process has evolved independently at least twice in prokaryotes given that gram-negative and gram-positive bacteria have distinct sets of chi sites and cognate exonuclease proteins (El Karoui *et al.* 2000).

An example of targeting homologous exchange *away* from particular regions of the genome comes from studies of mice, where recombination events might disrupt evolved combinations of transcriptional regulatory signals (Brick *et al.* 2012). A particular protein has evolved to recognize those combinations and suppress recombination events (Segurel *et al.* 2011). This same protein also protects the integrity of its own coding sequences (Jeffreys *et al.* 2013). Chromatin formatting plays an important role in regulating the distribution of homologous recombination sites (Yamada *et al.* 2013), and the same recombination suppressing protein also influences this epigenetic regulation (Grey *et al.* 2011).

Targeting mobile element insertions towards adaptively useful locations (and away from harmful regions). Protein–DNA and protein–protein interactions frequently target mobile element insertions to advantageous positions. Here we will look at only two of many examples.

The bacterial transposon Tn7 encoding antibiotic resistances provides a good prokaryotic example (Craig, 1991). When horizontal transfer introduces Tn7 into a new cell, DNA recognition by the multi-protein integration complex occurs at a specific chromosomal location where insertion has no deleterious effect on bacterial physiology. However, when a plasmid without Tn7 is leaving a cell that carries a chromosomal copy of the element, a different targeting protein becomes part of the transposition/integration complex. This particular protein binds to a DNA replication factor and targets new insertions in a sequence-independent manner to actively replicating DNA (Peters & Craig, 2001; Parks *et al.* 2009). As replication in the donor cell powers plasmid transfer events, this protein–protein interaction targets Tn7 insertions to mobilizing plasmids and facilitates dispersal of the transposon to new cells (Wolkow *et al.* 1996; Parks & Peters, 2009).

In yeast cells, there are a number of retroviral-like mobile elements that display distinctive insertion patterns determined by protein–protein interactions that keep them from disrupting expressed coding sequences but allow them to alter coding sequence expression (Levin & Moran, 2011):

(i) In budding yeast, retrotransposons Ty1 and Ty3 both insert upstream of RNA PolIII transcription start sites. However, the precise molecular mechanism is specific to each element. For Ty1, the integrase protein interacts with nucleosome histone markers at the initiation site (Mou *et al.* 2006; Mularoni *et al.* 2012), while the Ty3 integrase interacts with two PolIII transcription initiation factors (Kirchner *et al.* 1995).
(ii) The budding yeast retrotransposon Ty5 inserts preferentially into unexpressed chromatin regions by binding of a phosphorylated domain of the integrase to the Sir4 silencing factor (Xie *et al.* 2001; Brady *et al.* 2008). However, under stress conditions, the phosphate is lost from the integrase domain, and insertion becomes untargeted, perhaps because insertions into expressed regions of the genome may prove useful (Dai *et al.* 2007).
(iii) In fission yeast, the Tf1 retrotransposon inserts upstream of RNA PolII transcription start sites due to interaction of the integrase protein with 5′-binding transcriptional activators (Behrens *et al.* 2000; Leem *et al.* 2008).

These distinct yeast retrotransposon targeting mechanisms with remarkably similar specificities appear to have evolved independently for adaptive utility.

Targeting isotype class switching by intercellular signalling. One example of NGE targeting that deserves emphasis is class switching in the DNA encoding immunoglobulins. This process occurs in activated B cells once VDJ joining and somatic hypermutation have generated and refined the antigen binding capacity of an immunoglobulin molecule (Bothmer *et al.* 2011).

Immunoglobulins originate as cell-bound IgM molecules because the constant region of the heavy protein chain is encoded by a μ exon (Fig. 1). Directing the antigen specificity of the immunoglobulin towards different locations in the body occurs by a change in the constant region of the heavy chain (H_C). This requires a 'class switch' of the encoding H_C exon from μ to one encoding another Ig class or 'isotype' (Fig. 1).

The isotype switch occurs by inducing DS breaks at special 'switch' regions (S) preceding each H_C exon at the immunoglobulin heavy chain (IgH) locus (black diamonds in Fig. 1) (Bothmer *et al.* 2013). The DS break requires transcription at S_μ (already transcribed) and a second switch region. The downstream switch regions each have a promoter responsive to a combination of lymphokine signalling molecules. As only activated and

transcribed switch regions undergo breaks followed by end-joining, the cells of the immune system effectively instruct the activated B cell which class/isotype antibody to synthesize.

The connection of transcription and DNA rearrangement is a powerful tool for directing NGE activities to any functionally regulated region of the genome.

Genome homeostasis and cancer

One implication of the RW genome concept is that cells have elaborate regulatory circuits controlling NGE activities so the genome is not disrupted during normal reproduction.

We observe homeostatic control of highly evolved NGE systems where complex DNA rearrangement processes occur only in certain tissues, such as vertebrate adaptive immune systems, and where specific DNA changes occur only at defined stages of the life cycle, such as bacterial sporulation (Stragier *et al.* 1989; Kunkel *et al.* 1990), cyanobacterial heterocyst differentiation (Carrasco & Golden, 1995; Golden & Yoon, 1998), yeast mating-type switches following spore germination (Haber, 2012) and massive post-mating genome restructuring in ciliated protozoa (Prescott, 2000) (http://shapiro.bsd.uchicago.edu/Ciliate_macronuclear_development.html).

The RW genome perspective provides us with a new way of thinking about the high levels of genome change in cancer cells (Richards, 2001; Davies, 2013). Instead of considering stochastic mutations as *causes* of cell reprogramming in cancer, we can rather think of particular NGE system activations as *consequences* of oncogenic changes in cell regulatory networks.

Activation of specific NGE functions may help to explain some of the recurrent DNA rearrangement patterns observed in particular kinds of tumours, exemplified by the Philadelphia chromosome in chronic myelogenous leukaemia (CML) (Rowley, 1973, 2008). In the case of lymphomas due to aberrations of immune system rearrangements, the identity of the specific NGE operator can be determined (Nambiar & Raghavan, 2011; Rocha *et al.* 2012; Rocha & Skok, 2013).

It is notable that genome changes become more extensive as cancer progresses (Jeggo, 2005; Alexandrov *et al.* 2013). Tumours exemplify the extreme kinds of genome changes cells can produce when normal regulation of NGE radically fails. This failure can lead to activation of genome change programmes that generate novel cell proliferation phenotypes (Davies, 2013). The phenomenon of 'chromothripsis' (literally, chromosome shattering) is particularly interesting (Kloosterman *et al.* 2011; Chen *et al.* 2012; Korbel & Campbell, 2013). In chromothripsis, individual chromosomes are fragmented and rearranged, sometimes in a new structure or sometimes with pieces transposed to other chromosomes. Such extreme genome rearrangements resemble some of the chromosome scrambling observed when related genomes are compared, such as human and mouse (Waterston *et al.* 2002; Armengol *et al.* 2003). Perhaps the rapid occurrence of similar scrambling in cancer has lessons for evolutionary biology.

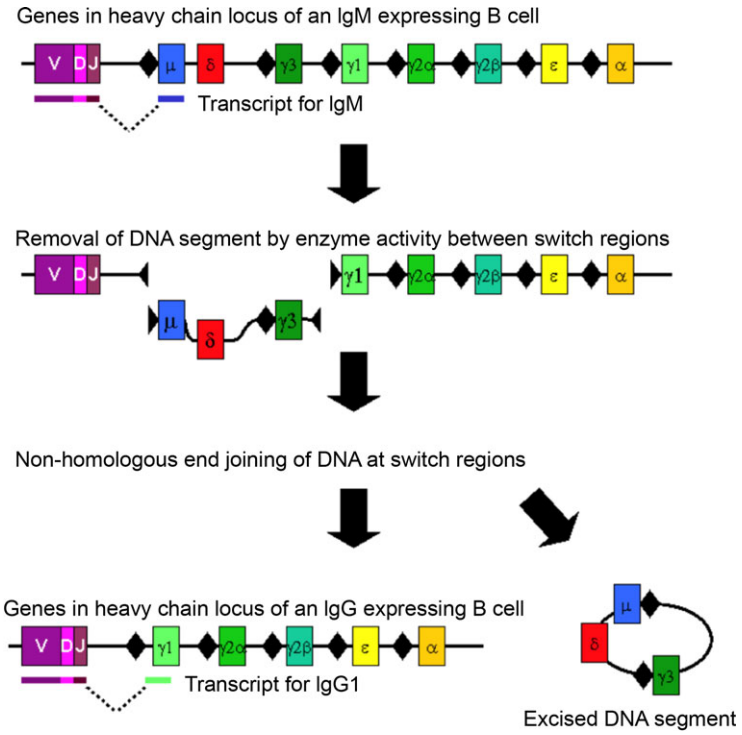

Figure 1. Mechanism of class switch recombination that allows isotype switching in activated B cells
The boxes indicate exon cassettes and black diamonds indicate switch regions. Copied from Wikipedia and used according to Wikimedia Free Commons.

Another lesson of chromothripsis is that NGE events can often occur multiple times in spatially restricted domains, such as a single chromosome. One aspect of RW genome changes is that regulatory interactions can intersect with NGE functions (Lin *et al.* 2009). This possibility has been suggested for the chromosome looping effect of androgen receptors on the location of recurrent rearrangement breakpoints in prostate cancer (Wu *et al.* 2011; Barbieri *et al.* 2012; Martin *et al.* 2013). We have seen transcription factor-mediated NGE targeting with yeast retrotransposons, and cancer genomics may well provide further examples.

A physiological view of the RW genome, its maintenance and differentiation

The preceding sections have attempted to make two major arguments: (i) the concept of an RW genome altered by cell action is more compatible with the discoveries of molecular genetics than the pre-DNA idea of a read-only memory (ROM) subject to accidental change; (ii) the concepts of physiological regulation can be applied to the control of the NGE operators that alter DNA sequences and genome structure in non-random and controlled ways.

With respect to genome maintenance, the parallels appear to be straightforward between homeostatic regulation of organismal physiology and the phenomenology of genome proofreading, DNA repair and inhibition of NGE functions during normal reproduction. However, the same parallel is applicable to a ROM memory view of the genome.

Where the idea of an RW genome diverges from conventional thinking in both genetics and physiology is in the realm of genome differentiation. In this case, regulation is for change rather than for stability. Genomes can change to take on specialized tasks that occur repeatedly in the life cycle or for adaptive innovation in the face of evolutionary challenges.

We know that the genome changes as part of the normal life cycle fit into organismal physiology in the same way as cellular, tissue and morphological differentiation do in multicellular development. Normal life-cycle genome changes occur under well-defined conditions and have characteristic features, even if the functional purpose is to generate diversity, as in the adaptive immune system and its antagonist, antigenic variation of infectious organisms (http://shapiro.bsd.uchicago.edu/ExtraRefs.NaturalGeneticEngineeringPartNormalLifeCycle.shtml). The existence of highly evolved and tightly regulated NGE processes that generate genome changes in a predictable fashion is an empirical reality incompatible with the ROM genome view.

The major challenge we face in understanding non-random genome change is its success in generating complex adaptive evolutionary innovations (Shapiro, 2011). It is not difficult to see how horizontal DNA transfer, domain shuffling and mobile element dispersal of regulatory signals expedite the search of functional genome space and thereby facilitate the evolution of novel biochemical activities and coordinately regulated networks.

Nonetheless, constructing the genomic basis for a major adaptive evolutionary innovation, such as a novel form of mimicry or a four-chambered heart, comprises coordinated changes in multiple developmental processes. How could that be accomplished? We know from studies of activation and targeting of NGE activities that genome change operators and cell regulatory circuits interact in multiple ways. A major 21st century research challenge for the life sciences (including physiology, molecular genetics and genomics) will be to explore the depth of control circuit–NGE interactions and learn how 'informed' the process of genome rewriting may be. I predict that big surprises are in store for all of us.

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Additional information

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